

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

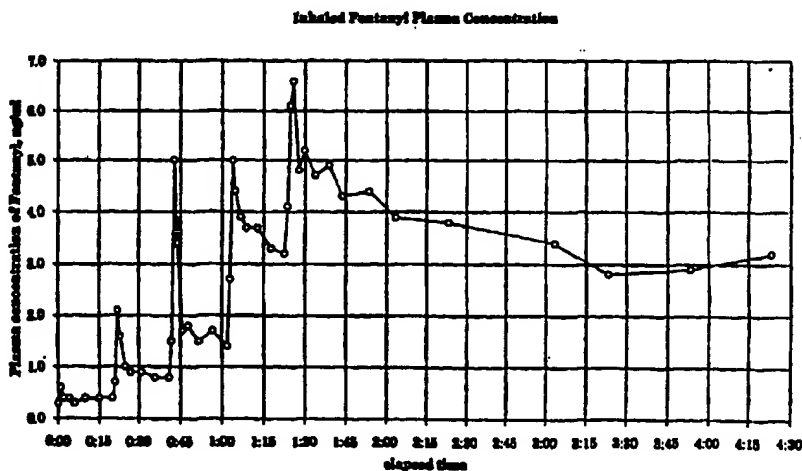
**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/12		A1	(11) International Publication Number: WO 95/31182
			(43) International Publication Date: 23 November 1995 (23.11.95)
(21) International Application Number: PCT/US95/05798		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(22) International Filing Date: 10 May 1995 (10.05.95)			
(30) Priority Data: 08/242,223 13 May 1994 (13.05.94) US			
(71) Applicant: ARADIGM CORPORATION [US/US]; 26219 Eden Landing Road, Hayward, CA 94545 (US).		Published With international search report.	
(72) Inventors: FARR, Stephan, J.; Welsh School of Pharmacy, Redwood Building, King Edward VII Avenue, Cathays Park, Cardiff CF1 3XF (GB). ROWE, Anthony, M.; Welsh School of Pharmacy, Redwood Building, King Edward VII Avenue, Cathays Park, Cardiff CF1 3XF (GB). RUB-SAMEN, Reid; 26219 Eden Landing Road, Hayward, CA 94545 (US).			
(74) Agent: BOZICEVIC, Karl; Fish & Richardson P.C., Suite 100, 2200 Sand Hill Road, Menlo Park, CA 94025 (US).			

(54) Title: NARCOTIC CONTAINING AEROSOL FORMULATION



(57) Abstract

An aerosol formulation is disclosed which is comprised of (and may consist essentially only of) an aerosol propellant and a base form of a narcotic drug selected from the group consisting of fentanyl, sufentanil, and remifentanyl. Such a formulation allows for the drug to be dissolved within the propellant and used within a device which does not require the use of a lubricant. Formulations are also disclosed which include lubricants, wherein the lubricant and propellant are both either polar or both non-polar. Thus, the lubricant component does not act as a solvent or cosolvent, but rather acts as a lubricant for the valve used for dispersing the formulation to a patient. Typical non-polar propellants include chlorofluorocarbons, which are typically used in connection with non-polar lubricants such as saturated vegetable oils, e.g. fractionated coconut oils. Typical polar propellants include hydrofluoroalkanes, which are typically used in connection with polar lubricants such as polyethylene glycols.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

-1-

5 NARCOTIC CONTAINING AEROSOL FORMULATIONField of the Invention

 This invention relates generally to narcotic
formulations useful in pain management. More
10 specifically, this invention relates to formulation of a
narcotic in a low boiling point propellant useful for the
intrapulmonary delivery of narcotics to a human patient.

Background of the Invention

15 Narcotic therapy forms the mainstay of pain
management. Narcotics can be administered in many forms
to patients with postsurgical and other forms of acute
and chronic pain. Morphine, one of the oldest narcotics,
is available for administration in tablet or in
20 injectable form. Fentanyl, a synthetic narcotic, was
first synthesized in 1960 by Paul Janssen and found to be
150 times more potent than morphine [Theodore Stanley,
"The History and Development of the Fentanyl Series,"
Journal of Pain and Symptom Management (1992) 7:3
25 (suppl.), S3-S7]. Fentanyl and its relatives Sufentanil
and Alfentanil are available for delivery by injection.
In addition, fentanyl is available for administration by
a transdermal delivery system in the form of a skin patch
[Duragesic™ (fentanyl transdermal system) package insert,
30 Janssen Pharmaceutica, Piscataway, NJ 08855, Jan-Jun
1991].

 A feature of the synthetic narcotic fentanyl is
that it has a more rapid time to onset and a shorter
duration of action than morphine. This makes fentanyl a
35 useful drug for the management of acute pain. Currently,

-2-

fentanyl is typically given by intravenous injection for acute pain management. Although fentanyl can be given by a transdermal patch, transdermal delivery of fentanyl is designed for long-term administration of the drug and
5 does not lend itself to achieving a peak level rapidly for a short-term effect.

An alternative to delivery by injection for narcotics is delivery by inhalation. Morphine [J. Chrusbasik et al., "Absorption and Bioavailability of
10 Nebulized Morphine," *Br. J. Anaesth.* (1988) 61, 228-30], fentanyl [M.H. Worsley et al., "Inhaled Fentanyl as a Method of Analgesia," *Anaesthesia* (1990) 45, 449-51], and sufentanil [A.B. Jaffe et al., "Rats Self-administer
15 Sufentanil in Aerosol Form," *Psychopharmacology*, (1989) 99, 289-93] have been shown to be deliverable as aerosols into the lung. The pilot study described by Worsley suggested that "inhaled fentanyl is an effective, safe and convenient method of analgesia which merits further investigation."

20 Inhalation of a potent synthetic narcotic aerosol provides a mechanism for the non-invasive delivery of rapid-acting boluses of narcotic. The on-demand administration of boluses of narcotic coupled with a controlled baseline intravenous infusion of narcotic is
25 termed "patient-controlled analgesia" (PCA) and has been found to be a very effective means of postoperative pain management.

Demand analgesia was first introduced in 1968 by Schetzer who showed it to be an effective mechanism
30 for treating postoperative patients [Maureen Smythe, "Patient-Controlled Analgesia: A Review," *Pharmacotherapy* (1992), 12:2, 132-43]. Prior to the availability of patient-controlled analgesia, the
35 paradigm for postoperative pain management consisted of intermittent intramuscular injections of narcotic. The

-3-

cycle of the patient feeling pain, calling the nurse who then must locate and bring the drug to the bedside for administration results in suboptimal postoperative pain management [Philip Shade, "Patient-controlled Analgesia: Can Client Education Improve Outcomes?," *Journal of Advanced Nursing* (1992) 17, 408-13].

Postoperative pain management by intermittent narcotic administration has been shown to be a largely ineffective method of pain management for many of the patients undergoing the more than 21 million surgical procedures in the United States each year [John Camp, "Patient-Controlled Analgesia," *AFP* (1991), 2145-2150]. Even if every patient reliably received a constant dose of narcotic postoperatively, studies of therapeutic narcotic pharmacokinetic data have shown that patient variability makes such an approach fundamentally unsound and potentially dangerous [L.E. Mather, "Pharmacokinetics and Patient-Controlled Analgesia," *Acta Anaesthesiologica Belgica* (1992) 43:1, 5-20].

The first commercial device for automatically providing intravenous patient-controlled analgesia was developed in Wales in the mid-1970s. This device, the Cardiff Palliator (Graesby Medical Limited, United Kingdom) is the predecessor of numerous currently available computer-controlled patient-controlled analgesia intravenous pumps [Elizabeth Ryder, "All about Patient-Controlled Analgesia," *Journal of Intravenous Nursing* (1991) 14, 372-81]. Studies using these computer controlled intravenous narcotic infusion pumps have shown that small doses of narcotics given on demand by the patient provided superior pain relief when compared with intermittent intramuscular administration of these drugs [Morton Rosenberg, "Patient-Controlled Analgesia," *J. Oral Maxillofac Surg* (1992) 50, 386-89].

35

- 4 -

These computer-controlled pumps typically allowed for the programming of four different parameters: 1) basal intravenous narcotic infusion rate; 2) the bolus of narcotic to be delivered on each patient demand; 3) the maximum hourly total dose of narcotic to be allowed; and 4) the lockout period between doses. Typical programming for postoperative pain management with intravenous fentanyl might be a basal infusion rate of 20 $\mu\text{g/hr}$, a bolus demand dose of 20 μg , a maximum hourly dose of 180 μg , and a lockout period between doses of 5 minutes. In a study of 30 patients treated for postoperative pain with intravenous fentanyl patient-controlled analgesia, the minimum effective concentration (MEC) of fentanyl in the blood required to achieve pain relief in the group of patients studied was found to range from 0.23 to 1.18 ng/ml. Clinically significant respiratory depression was not seen in this study consistent with published data indicating that a fentanyl concentration of 2 ng/ml in the blood is typically required to depress the respiratory rate [Geoffrey Gourlay et al., "Fentanyl Blood Concentration — Analgesic Response Relationship in the treatment of Postoperative Pain," *Anesth Analg* (1988) 67, 329-37].

The administration of narcotic for pain management is potentially dangerous because overdoses of narcotics will cause complications such as respiratory depression. The patient's respiratory rate is decreased by the administration of narcotics. This decrease in respiratory rate may not be associated with a change in respiratory tidal volume [Miller, *Anesthesia* (2nd ed), Churchill Livingstone, I, 762]. The four programmable parameters available on computer-controlled intravenous patient-controlled analgesia infusion pumps must be selected so as to minimize the likelihood of narcotic overdose. The preferred technique is to set the basal

-5-

infusion rate at a relatively low rate and increase this rate based on how many times the patient presses the bolus demand button to self-administer supplemental drug.

As long as the patient himself or herself is the only one to push the demand button, respiratory depression is unlikely. However, there have been documented cases of the patient's family and friends pressing the narcotic demand button, for instance, while the patient is sleeping [Robert Rapp et al., "Patient-controlled Analgesia: A Review of the Effectiveness of Therapy and an Evaluation of Currently Available Devices," *DICP, The Annals of Pharmacotherapy* (1989) 23, 899-9040].

It is a problem with patient-controlled analgesia that it must currently be performed using an intravenous infusion pump. This requires that an indwelling catheter be placed in the patient's vein and that the patient transport a relatively bulky system with himself at all times to receive a baseline infusion of intravenous narcotic and allow for intermittent on-demand self-bolusing of additional narcotic in order to match the patient's changing need for drug. A portable PCA device incorporating a wristwatch-like interface has been described [D.J. Rowbotham, "A Disposable Device for Patient-Controlled Analgesia with Fentanyl," *Anaesthesia* (1989) 44, 922-24]. This system incorporated some of the features of computer-controlled programmable PCA infusion pumps such as basal infusion rate and the amount of each bolus. However, this system, which involved the use of an intravenous catheter as seen in larger infusion pumps, incorporated no provision to record accurately the actual dose of fentanyl administered to the patient over time.

Although fentanyl can be administered by transdermal patch, this method has been found to be suboptimal for postoperative pain management [K.A.

-6-

Lehmann et al., "Transdermal Fentanyl for the Treatment of Pain after Major Urological Operations, *Eur. J. Clin Pharmacol* (1991) 21:17-21]. Lehmann found that the low dose of narcotic delivered by transdermal fentanyl was inadequate to provide pain relief to many of his patients and that boosting the baseline infusion rate of the patch would put some patients at risk for having significant respiratory depression. In addition, he points out that if such a complication were to appear in conjunction with the delivery of narcotic by transdermal patch, the infusion could not be quickly stopped because the "cutaneous fentanyl depot" created by the transdermal patch would cause narcotic infusion to continue even after removal of the patch.

Delivery of fentanyl by aerosol used in conjunction with a non-invasively delivered long-acting preparation of narcotic such as slow-release oral morphine or a fentanyl transdermal patch provides a means for non-invasive administration of a basal rate of narcotic and rapid-acting boluses of narcotic to an ambulatory patient.

It is a problem with the aerosol delivery of fentanyl previously described that inefficient, bulky nebulizers must be used for the administration of the drug. In addition, these nebulizers work by administering from an open reservoir of the drug in aqueous solution allowing the vapor to be generally distributed and creating the potential for overdosing due to the lack of reproducible aerosol delivery. In addition, abuse through theft of the aqueous-phase fentanyl and subsequent unauthorized repackaging of this controlled substance in an aqueous injectable form are possible.

Because most surgery today is being done on ambulatory patients and because these patients are often

-7-

rapidly discharged from the hospital and because patient-controlled analgesia has been identified as the preferred method of postoperative pain management, it is desirable to have a safe and effective method for non-invasive, ambulatory patient-controlled analgesia.

One attempt at providing a fentanyl containing aerosol formulation is disclosed within WO 90/0733 published July 12, 1990 which teaches that in order to produce fentanyl containing aerosol compositions it is necessary to use a co-solvent and a surface active agent. The surface active agent is coated onto fentanyl and the co-solvent is combined with the propellant in order to create the formulation.

Summary of the Invention

An aerosol formulation is disclosed which is comprised of (and may consist essentially only of) an aerosol propellant and a base form of a narcotic drug selected from the group consisting of fentanyl, sufentanil, and remifentanyl. Such a formulation allows for the drug to be dissolved within the propellant and used within a device which does not require the use of a lubricant. Formulations are also disclosed which include lubricants, wherein the lubricant and propellant are both either polar or both non-polar. Thus, the lubricant component does not act as a solvent or cosolvent, but rather acts as a lubricant for the valve used for dispersing the formulation to a patient. Typical non-polar propellants include chlorofluorocarbons, which are typically used in connection with non-polar lubricants such as saturated vegetable oils, e.g. fractionated coconut oils. Typical polar propellants include hydrofluoroalkanes, which are typically used in connection with polar lubricants such as polyethylene glycols.

- 8 -

A primary object of the invention is to provide an aerosol formulation consisting essentially of a propellant and a free base form of narcotic selected from the group consisting of fentanyl, sufentanil, and remifentanyl.

A feature of the invention is that the formulation does not include and does not require a co-solvent or surface active agent.

An advantage of the present invention is that only the minimum components necessary to propel the narcotic from the container and provide for the analgesic effect desired are present within the formulation.

Another advantage of the invention is that the formulation can be administered to obtain a particularly fast acting analgesic effect.

Another advantage is that the formulation can be used to provide an analgesic effect to ambulatory patients within seconds after being administered.

Another important object of the invention is to provide an aerosol formulation consisting essentially of a propellant, a free base form of a narcotic and a lubricant wherein the lubricant and propellant are both polar or both non-polar.

Another feature of the invention is that formulations containing no lubricant are dispersed from devices wherein the valve does not require a lubricant whereas formulations containing lubricant can be dispersed from any valve type.

Another advantage of the formulations of the invention is that the narcotic drug dissolves within the propellant without the need for a surfactant or co-solvent to form a formulation which does not include agglomeration of particles.

These and other objects, advantages and features of the present invention will become apparent to

-9-

those skilled in the art upon reading this disclosure in combination with drawings wherein like numerals refer to like components throughout.

5 Brief Description of the Drawing

Figure 1 is a graph showing the results of an experiment plotting time vs. plasma level of fentanyl obtained with the invention.

10 Detailed Description of the Preferred Embodiments

Before the present formulations used in pain management used in connection with the invention are described, it is to be understood that this invention is not limited to the particular methodology, devices and
15 formulations described, as such methods, devices and formulations may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention
20 which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a
25 formulation" includes mixtures of different formulations, reference to "an antagonist" includes a plurality of such compounds, and reference to "the method of treatment" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

30 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described
35 herein can be used in the practice or testing of the

-10-

invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe and disclose specific information for which the reference was cited in connection with.

The terms "analgesic drug" and "narcotic drug" are used interchangeably herein and shall be interpreted to mean a free base form of a drug selected from the groups consisting of fentanyl, sufentanil, and remifentanyl.

Terms such as "propellant", "aerosol propellant", "low boiling point propellant" and the like are used interchangeably herein to describe compounds generally used in connection with metered dose inhalers which compounds are liquified under pressure (many are gaseous at normal atmospheric pressure and temperature) and include chlorofluorocarbons, hydrofluorocarbons, hydrochlorofluorocarbons, hydrochlorocarbons, hydrocarbons, and hydrocarbon ethers.

The term "consisting essentially only of" is used herein to describe components of a formulation and shall mean that the formulation contains the specific components recited and contains less than 0.05% by weight of other components intentionally added and that the formulation may include minor acceptable levels of contaminant components in an amount of less than 0.05% by weight. The term excludes components intentionally added such as co-solvents and/or surface active agents which might be added to dissolve a drug and/or disperse drug particles (added for these normal functions). Formulations of the invention may consist essentially only of propellant, drug and a lubricant provided that the lubricant and propellant are both either polar or non-polar.

-11-

The terms "polar" and "non-polar" are used herein to describe the relative functional characteristics of one compound to another and specifically to define the solubility characteristics of the lubricant relative to the propellant. Polar lubricants are added to polar propellants and non-polar lubricants are added to non-polar propellants. Polar lubricants will dissolve readily in polar propellants and non-polar lubricants will dissolve readily in non-polar propellants. However, a polar lubricant will not have any or any significant effect on the solubility of the narcotic drug within the polar lubricant. Further, a non-polar lubricant will not have any or any significant effect on the solubility of a narcotic within a non-polar propellant. Thus, the lubricants are added only so as to provide lubrication to a valve and do not act as co-solvents or surfactants within the formulation and have no or no significant effect on the solubility of the narcotic within the propellant. The solubility characteristics of compounds such as lubricants and propellants are determined chiefly by their polarity. Non-polar or weakly polar lubricants dissolve in non-polar or weakly polar propellant solvents. Highly polar lubricants dissolve in highly polar propellant solvents -- thus, like dissolves like. When a lubricant is added to a propellant both the lubricant and the propellant have the same or a sufficiently similar polarity (both are polar or both are non-polar) such that the lubricant does not act as a cosolvent, dispersing agent or surfactant. Accordingly, the lubricant will have no effect and/or a negligible effect on the solubility of the narcotic drug within the propellant. In accordance with a strict conventional definition of polar a molecule is polar if the center of negative charge does not coincide with the center of positive

-12-

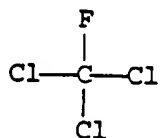
charge. Although our definition does not negate the strict conventional definition we expand such to indicate that a polar lubricant will dissolve within a polar propellant without any or any significant effect on the solubility of narcotic within the propellant e.g. the lubricant would have an effect of 20% or less on the solubility of narcotic drug within the propellant, preferably 10% or less and most preferably 0%.

10 Formulation in General

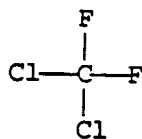
Aerosol formulations disclosed are solutions, not suspensions, which consist essentially only of a low boiling point propellant and a free base form of a narcotic drug and a low boiling point propellant. The narcotic drug is a pharmaceutically pure free base form of a drug selected from the fentanyl, sufentanil, or remifentanyl.

Formulations consisting only of propellant and drug must be used in connection with devices which include valves which valves do not require a lubricant. Other formulations of the invention include a lubricant in relatively small amounts e.g. in the range of 0.01% to 0.5% by weight. When a lubricant is present the lubricant and the propellant are both polar or are both non-polar. Thus, the lubricant does not act as a co-solvent or surfactant within the formulation.

Specific low boiling point propellants have been found to be particularly useful in creating formulations of the invention. These propellants are as follows:

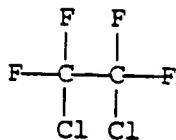


Formula I

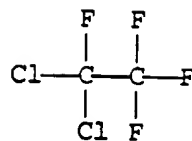


Formula II

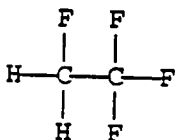
-13-



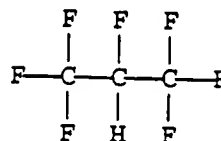
Formula III



Formula IV



Formula V



Formula VI

The narcotic drug component is added to the propellant component as a dry powder. The dry powder includes particles which dissolve in and form a solution with the propellant. The narcotic drug component may comprise as much as 5% of the formulation (solution) but is generally present in an amount of 0.5% by weight or less based on the volume of the total formulation, i.e. the combination of the propellant and narcotic drug. In general, the narcotic will be present in the formulation in an amount of about 0.5% to 0.01% by volume.

The narcotic drug is combined with the propellant and included within a pressurized aerosol inhaler container of the type generally used in connection with metered dose inhalers (MDIs). The container includes a valve which upon opening will release a metered dose of formulation. When released the propellant within the formulation will "flash" and become mostly gaseous, leaving a small amount of supercooled propellant and the particles of narcotic drug. The remainder of the propellant evaporates as it moves toward the lungs so that only particles will be delivered to the patient.

The formulation does not include cosolvents and/or surfactants in useful amounts, i.e. amounts such that the cosolvent could or does effect the ability of

-14-

the drug to dissolve in the propellant solvent and/or cause particles to intermix therein in a uniform dispersion. The ability to create a formulation wherein the narcotic drug is uniformly dissolved within the propellant without using any cosolvent and/or surfactant is a particularly important aspect of the present invention. Accordingly, further explanation is provided below.

When a formulation of the invention includes only the propellant and no solvents or surfactants, the formulation is used in connection with a valve which does not require any lubricant. An example of such a valve is BK 357 available commercially from Bepak. The valve has been shown to provide for reproducible metering of doses of drug released from a conventional metered dose inhaler when using various conventional propellants, including chlorofluorocarbons, hydrofluorocarbons, 134a, and blends of hydrofluorocarbons with ethanol. Those skilled in the valve art will understand that formulations of the invention which include only the propellant and drug dissolved therein can be used in connection with other valves, provided those valves are designed to operate without the use of a lubricant. It is pointed out that, when the salt form of a drug such as fentanyl citrate is formulated with a propellant without the use of a cosolvent and/or surfactant, the resulting formulation creates a suspension composed of overtly agglomerated particles of drug which is essentially not usable in a conventional metered dose inhaler. However, by using the base form of the drug as per formulations described herein, it is possible to obtain formulations wherein the drug is dissolved in the propellant.

It is known that, in order for a surfactant component to act as a surfactant, a polar molecule will be used in combination with a non-polar solvent. For

-15-

example, the polar molecules within conventional soap act as surfactants with respect to the non-polar molecules in oil. Based on this conventional thinking, a conventional formulation will use a polar surfactant and/or cosolvent when the propellant solvent is non-polar. Alternatively, when the propellant is polar, the surfactant and/or cosolvent is non-polar. Thus, conventional formulations use solvents and/or surfactants for their conventional effect of intermixing the propellant with the drug which eliminates the agglomeration of drug particles and provides for a more uniform formulation which can be dispersed from a conventional metered dose inhaler device.

Formulations of the present invention do not require the use of surfactants and/or cosolvents. However, if the formulation is to be used with a valve which requires lubrication, the lubricant should be included within the formulation. The lubricants included are not being included as cosolvents and/or surfactants. Specifically, when the formulation is one which includes a propellant which is non-polar, such as a chlorofluorocarbon, the lubricant used is also non-polar. Thus, the non-polar lubricant does not act as a conventional surfactant and/or cosolvent. Examples of such non-polar lubricants to be used with non-polar propellants are saturated vegetable oils, for example, a series of fractionated coconut oils available commercially as Miglyol 812, 829 and 840. Other vegetable oils and/or non-polar molecules conventionally used as lubricants could also be included within the formulation when non-polar propellants are used to formulate.

When a formulation of the invention is prepared using a polar propellant such as a hydrofluoroalkane (HFA) and the formulation is used in a device having a valve which requires a lubricant, the formulation will

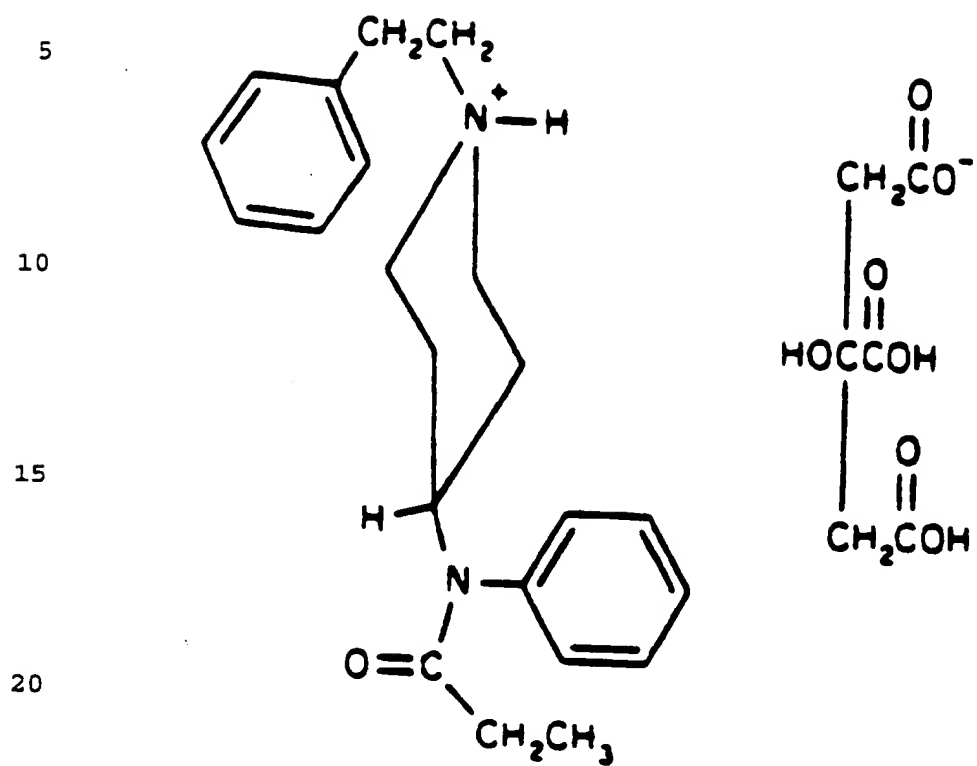
-16-

include a polar lubricant such as polyethylene glycol, examples of which are available as PEG 100, 200, 300, 400, 600, 1000, and 1500. Other polar molecules with lubricating properties could also be used in connection with formulations of the invention wherein the propellant is comprised of polar molecules.

Based on the above, it can be seen that formulations of the invention may include no cosolvents and/or surfactants and be used in connection with valves which do not require lubricants. However, the formulations may include compounds which might at first appear to have other functions, but which are actually acting only as valve lubricants. The lubricants provided within the formulations are polar when the propellant solvent is polar, and the lubricants are non-polar when the propellant solvent is non-polar. Thus, the lubricants do not provide for a cosolvent and/or surfactant effect within the formulation, and are present only in amounts sufficient to provide for valve lubrication when they are used in connection with valves which require a lubricant. The lubricant and propellant are sufficiently similar regarding their polarity that the lubricant has no or substantially no effect as a cosolvent and/or dispersant i.e. does not effect the solubility and/or dispersability of the drug in the propellant.

The drug particles consist essentially only of the narcotic drug i.e. the free base form (and not the salt form) of a drug selected from the group consisting of fentanyl, sufentanil, and remifentanyl. Narcotic drugs such as these are normally present and formulated in their salt form. For example, fentanyl is normally present as fentanyl citrate which is shown below:

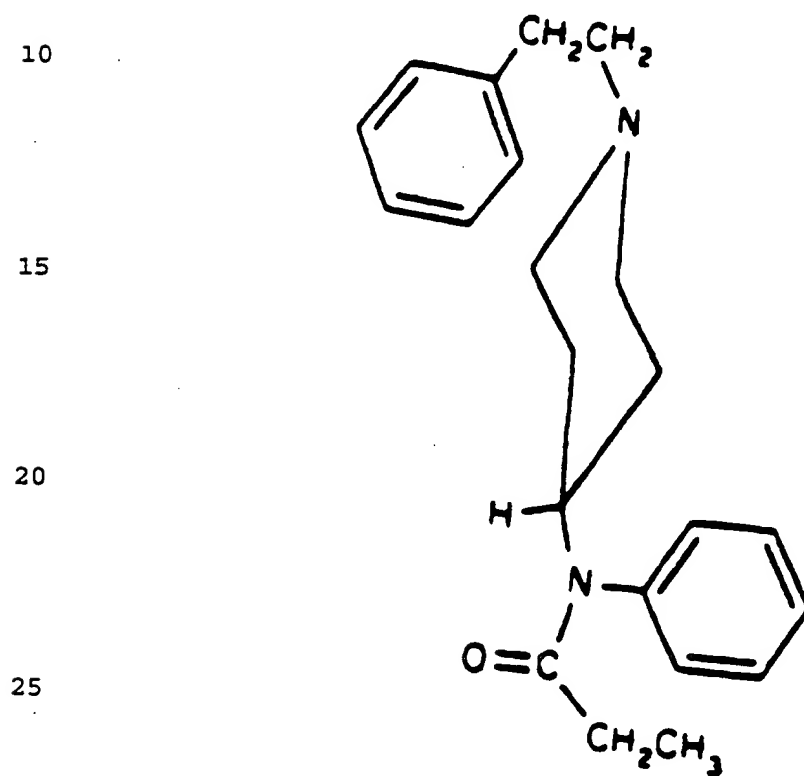
-17-



Fentanyl Citrate
Formula VII

-18-

In accordance with processing disclosed herein
the citrate form or other salt form of fentanyl may be
used to obtain the free base form of the drug used in
formulations of the present invention. The free base
5 form of fentanyl is shown below:



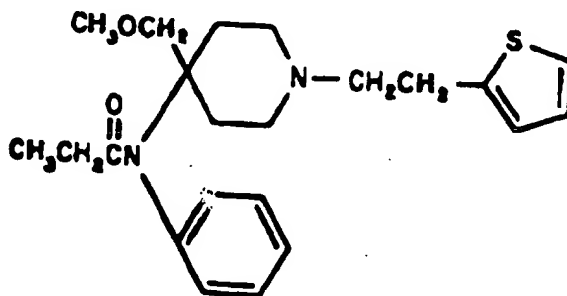
Fentanyl Free Base
Formula VIII

35

-19-

With respect to each of the narcotic drugs the salt form is generally used as a starting material. The salt form is then processed in order to obtain the free base of the drug. The free base form of the drug is dissolved in a propellant to provide a drug/propellant solution which is the formulation of the present invention. If the free base form of the drug is not created then it will not be possible to dissolve the drug in the propellant and create the formulation without the use of co-solvents and/or surfactants in relatively high amounts.

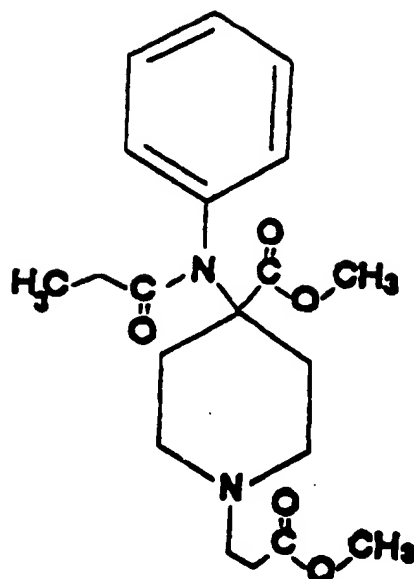
The structural formula of the free base form of other preferred narcotic drugs used in connection with the present invention are shown below. Preferred narcotic drugs include the free base form of fentanyl, sufentanil, and remifentanyl with remifentanyl being particularly preferred due to its fast-acting narcotic effect.



Sufentanil Free Base

Formula IX

-20-



Remifentanyl Free Base

Formula X

Preparation of Narcotic Free Base

The free base form of various narcotic drugs are shown above. This free base form of the drug is, in general, created by using the salt form, such as fentanyl citrate, as the starting material. The salt form of the drug is dissolved in water and then combined with a strong base such as ammonia which, in water, forms ammonium hydroxide. It is possible to precipitate out the free base form of the drug from such a solution. Thereafter, various purification processing is carried out in order to obtain pharmaceutically pure drug in the free base form. It is the pure form of the free base drug which is combined with a propellant in order to form formulations of the present invention.

-21-

Propellants

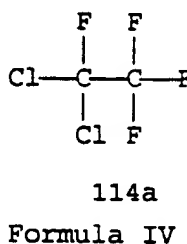
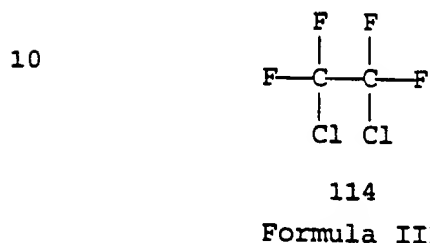
Propellants used in connection with the
interpulmonary delivery of drugs are described by using
two or three digits. When two digits are present the
5 first digit is assumed to be zero. The first digit is
one less than the number of carbon atoms in the compound.
Accordingly, if the first digit is one in a three digit
number the compound includes two carbon atoms. If the
propellant is designated by only two digits the first
10 digit is assumed to be zero and the compound includes
only a single carbon atom. The second digit describing
the propellant is one more than the number of hydrogen
atoms in the compound. Accordingly, if the second digit
is one the compound includes no hydrogen atoms. The
15 third and last digit represents the number of fluorine
atoms in the compound.

The above information can be used to determine
the chemical composition of any propellant described by
three digits when the propellant is comprised of carbon,
20 hydrogen and fluorine atoms. However, some propellants
also include chlorine atoms. The number of chlorine
atoms in the compound is found by subtracting the sum of
the fluorine and hydrogen atoms from the total number of
atoms which can be added to saturate the carbon chain.
25 Thus, a propellant described as 114 indicates that the
propellant includes two carbon atoms. The second 1 in
the number indicates that the compound includes 0
hydrogen atoms. The third digit "4" indicates that the
compound includes four fluorine atoms. Since two carbon
30 atoms would be saturated with the presence of six
attached atoms the propellant must include two chlorine
atoms.

Some propellants are isomers of each other.
When isomers exist the propellant compound which is the
35 most symmetric compound is indicated by a number by

-22-

itself. The isomer closest to that structure is indicated by the letter "a" following the number. As the degree of asymmetry increases the letters "b", "c" etc. are added. For cyclic compounds a "C" is used in front of the number. In order to show an example of two propellants which are isomers of each other the following structural formulas are provided for propellants 114 and 114a:



15

Specific Formulations

Specific formulations of the invention are created by first creating the free base form of the drug as described generally above and as described specifically in Example 1. The free base form of the drug, in a dry powder state is dissolved in a propellant. Thereafter, for some formulations, a valve lubricant (non-polar or polar) is added. Examples of some useful formulation are as follows wherein all percentages are by weight.

25

Formulation #1

fentanyl free base	1.0%
propellant 227	99.0%

30

Formulation #2

sufentanil free base	0.2%
propellant 134a	99.8%

35

-23-

Formulation #3

fentanyl free base	0.1%
propellant 11 & 12 in 28:72 blend	99.9%

5

Formulation #4

remifentanyl free base	0.01%
propellant 227	99.99%

10

Formulation #5

fentanyl free base	0.02%
propellant 227 & 134a in 50:50 blend	99.98%

15

Formulation #6

fentanyl free base	0.95%
propellant (polar)	99.0%
lubricant (polar)	0.05%

20

Formulation #7

sufentanil free base	0.15%
propellant (non-polar)	99.8%
lubricant (non-polar)	0.05%

25

Formulation #8

fentanyl free base	0.1%
propellant (polar)	99.85%
PEG 300	0.05%

30

Formulation #9

remifentanyl free base	0.01%
propellant (non-polar)	99.94%
oil	0.05%

35

-24-

Formulation #10

sufentanil free base	0.02%
propellant (HFA polar)	99.93%
PEG 300	0.05%

5

Formulation #11

fentanyl free base	1.0%
propellant CFC	98.95%
Miglyol 812	0.05%

10

Formulation #12

sufentanil free base	0.2%
propellant (HFA)	99.75%
PEG 100	0.05%

15

Formulation #13

fentanyl free base	0.1%
propellant (blend of polar and non-polar)	99.9%

20

Formulation #14

remifentanyl free base	0.01%
propellant 114	99.94%
Miglyol 829	0.05%

25

Formulation #15

remifentanyl free base	0.02%
propellant 227 & 134a in 50:50 blend	99.98%

30

Formulation #16

fentanyl free base	0.95%
propellant (HFA)	99.0%
PEG 300	0.05%

35

-25-

Formulation #17

	sufentanil free base	0.15%
	propellant 134a	99.8%
5	Miglyol 840	0.05%

Formulation #18

	fentanyl free base	0.1%
	propellant 11 & 12 in 28:72 blend	99.85%
10	fractionated coconut oil	0.05%

Formulation #19

	remifentanyl free base	0.01%
	propellant 227	99.94%
15	saturated oil	0.05%

Formulation #20

	free base	0.02%
	propellant 227 & 134a in 50:50 blend	99.93%
20	lubricant	0.05%

Comparative FormulationsComparative #21 (no surfactant/cosolvent)

25	fentanyl citrate	15.71 mg
	Span 85	0
	p11	1.913 g
	p12	4.920 g
	total (5 ml)	6.849 g

Comparative #22 (0.05% surfactant)

30	fentanyl citrate	15.71 mg
	Span 85	3.42 mg
	p11	1.912 g
	p12	4.918 g
35	total (5 ml)	6.849 g

-26-

Comparative #23 (0.5% surfactant)

	fentanyl citrate	15.71 mg
	Span 85	34.2 mg
	p11	1.904 g
5	p12	4.845 g
	total (5 ml)	6.849 g

Unlike formulations of the present invention which included no surfactant and/or cosolvent, comparative formulation #21 (with no surfactant/ cosolvent) included overtly agglomerated particles.

Comparative Examples 22 and 23 are suspensions and not solutions. Examples 1-20 are solutions.

15 General Methodology

A non-invasive means of pain management is provided in a manner which makes it possible to maintain tight control over the amount of drug administered to a patient suffering with pain. The formulation is administered by intrapulmonary delivery in a controlled and repeatable manner. The formulation is preferably delivered from a device which is not directly actuated by the patient in the sense that no button is pushed nor valve released by the patient applying physical pressure. On the contrary, the device provides that the valve releasing analgesic drug is opened automatically upon receipt of a signal from a microprocessor programmed to send a signal when data is received from a monitoring device such as an airflow rate monitoring device. A patient using the device withdraws air from a mouthpiece and the inspiratory rate, and calculated inspiratory volume of the patient is measured one or more times in a monitoring event which determines an optimal point in an inhalation cycle for the release of a dose of analgesic drug. Inspiratory flow is measured and recorded in one

-27-

or more monitoring events for a given patient in order to develop an inspiratory flow profile for the patient. The recorded information is analyzed by a microprocessor in order to deduce a preferred point within the patient's
5 inspiratory cycle for the release of analgesic drug with the preferred point being calculated based on the most likely point to result in a reproducible delivery event.

The device preferably includes a flow rate monitoring device which continually sends information to
10 the microprocessor, and when the microprocessor determines that the optimal point in the respiratory cycle is reached, the microprocessor actuates the opening of the valve allowing release of analgesic drug. Accordingly, drug is always delivered at a pre-programmed
15 place in the inspiratory flow profile of the particular patient which is selected specifically to maximize reproducibility of drug delivery and peripheral deposition of the drug. It is pointed out that the device can be used to, and actually does, improve the
20 efficiency of drug delivery. However, this is not the critical feature. The critical feature is the reproducibility of the release of a tightly controlled amount of drug at a particular point in the respiratory cycle so as to assure the delivery of a controlled and
25 repeatable amount of drug to the lungs of each individual patient.

The combination of automatic control of the valve release, combined with frequent monitoring events in order to calculate the optimal flow rate and time for
30 the release of analgesic drug, combine to provide a repeatable means of delivering analgesic drug to a patient. Because the valve is released automatically and not manually, it can be predictably and repeatedly opened for the same amount of time each time or for the
35 preprogrammed measured amount of time which is desired at

-28-

that particular dosing event. Because dosing events are preferably preceded by monitoring events, the amount of analgesic drug released and/or the point in the inspiratory cycle of the release can be readjusted based on the particular condition of the patient. For example, if the patient is suffering from a condition which allows for a certain degree of pulmonary insufficiency, such will be taken into account in the monitoring event by the microprocessor which will readjust the amount and/or point of release of the analgesic drug in a manner calculated to provide for the administration of the same amount of analgesic drug to the patient at each dosing event.

It has been found that the ability to tightly control the amount of a volatile propellant formulation of drug delivered via the intrapulmonary route can be improved by delivering smaller doses of the propellant/drug formulation with each release of the valve and with each dosing event. Repeatability, in terms of the amount of analgesic drug delivered to a patient, is improved when the analgesic drug is delivered during a smooth, normal inhalation by the patient. To a certain extent, the ability to provide for a smooth inhalation is enhanced when smaller amounts of analgesic drug are released as compared with larger amounts of analgesic drug. Accordingly, an important aspect of the invention is to deliver aerosolized analgesic drug to a patient in a series of interrupted bursts while the patient continues a single inhaled breath, with each burst being delivered while the patient maintains optimal inspiratory flow.

The amount of analgesic drug delivered to the patient will vary greatly depending on the particular drug being delivered. In accordance with the present invention it is possible to deliver different narcotic

-29-

drugs. When sufentanil is administered it is generally administered to a patient in an amount in the range of about 10 μ g to 100 μ g. It is pointed out that sufentanil is approximately ten times more potent than fentanyl so that fentanyl is generally delivered to a patient in an amount of about 100 μ g to 1000 μ g. These doses are based on the assumption that when interpulmonary delivery methodology is used the efficiency of the delivery is approximately 10% and adjustments in the amount released must be made in order to take into account the efficiency of the device. The differential between the amount of analgesic drug actually released from the device and the amount of analgesic drug actually delivered to the patient varies due to a number of factors. In general, the device discussed above is approximately 20% efficient, however, the efficiency can be as low as 10% and as high as 50% meaning that as little as 10% of the released analgesic drug may actually reach the circulatory system of the patient and as much as 50% might be delivered. The efficiency of the delivery will vary somewhat from patient to patient and must be taken into account when programming the device for the release of analgesic drug. In general, a conventional metered dose inhaling device is about 10% efficient.

When administering analgesic drugs the entire dosing event can involve the administration of anywhere from 1 μ g to 100 mg, but more preferably involves the administration of approximately 10 μ g to 10 mg. The large variation in the amounts which might be delivered are due to the fact that different drugs have greatly different potencies and may be delivered from devices which vary greatly in terms of the efficiency of drug delivered. The entire dosing event may involve several inhalations by the patient with each of the inhalations

35

-30-

being provided with one or more bursts of analgesic drug from the device.

In addition to drug potency and delivery efficiency, analgesic drug sensitivity must be taken into consideration. The present invention makes it possible to vary dosing over time if analgesic sensitivity changes and/or if user compliance and/or lung efficiency changes over time.

Based on the above, it will be understood that the dosing or amount of analgesic drug actually released from the device can be changed based on the most immediately prior monitoring event wherein the inspiratory flow of a patient's inhalation is measured.

15

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make the formulations and use the methodology of the invention and are not intended to limit the scope of what the inventor regards as his invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviation should be accounted for. Unless indicated otherwise, parts or parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade and pressure is at or near atmospheric.

30

Example 1 Obtaining Fentanyl Free Base

The free base form of fentanyl can be obtained by using fentanyl citrate (purchased from Sigma Chemicals). First, dissolve 500 mg of fentanyl citrate in 100 ml of distilled water. Mixing should be thorough,

-31-

and is preferably carried out using sonification for approximately 60 seconds. Thereafter, adjust the pH of the solution to pH 10.0 by the dropwise addition of 2.5% v/v ammonium hydroxide solution. The free base form of fentanyl will precipitate out of solution as the pH is raised to approximately 10.0.

Transfer the solution to a 250 ml separating funnel. In order to ensure that all of the contents of the original beaker is transferred, wash the beaker with 25 ml of water and add the washings to the funnel. Wash the pH electrode, temperature probe and beaker with 25 ml of diethyl ether and add such to the separating funnel.

Add 100 ml of diethyl ether to the separating funnel. Thereafter, put a stopper in place and shake the contents. Thereafter, allow the contents to separate into two phases. Drain off and retain the lower aqueous phase. Transfer the organic layer to a weighed crucible cooled by resting on a bed of ice maintained at a temperature of approximately -15°C by a cooling plate. Return the aqueous layer to the separating funnel and add an additional 50 ml of diethyl ether. Include the stopper and shake again. Drain off and discard the aqueous layer. Transfer the organic layer to a crucible and allow the ether to evaporate.

If needed, the crucible can be placed in a vacuum oven at approximately 45-50°C overnight in order to thoroughly dry the residue. In order to confirm purity and yield, re-weigh the crucible to determine the residue weight. Carefully remove the residue from the crucible and weigh. Express this value as a percentage of the theoretical yield.

- 32 -

Example 2
Determine Purity

Obtain the fentanyl free base in a dried, pure form in accordance with the procedures described in Example 1. Determine the purity by making a sample of known weight in methanol and running against a standard curve. The standard curve is determined by making a dilution series from a fentanyl citrate/methanol solution which gives known concentrations of fentanyl base.

Example 3
Formulation Administration

Formulation consisting essentially only of fentanyl free base and propellant was delivered to a human patient. The patient was administered 50 μ l of formulation, which amount of formulation contained 100 μ g of fentanyl base. Accordingly, a patient was allowed to inhale a dose of 50 μ l of formulation from a device as shown within Figure 2 and described above.

The initial administration was of 100 μ g of fentanyl resulting in the release of 50 μ l of formulation. At intervals of 20 minutes, 40 minutes, 60 minutes and 80 minutes the patient was administered 200, 300, 400 and again 400 μ g of fentanyl base respectively. Accordingly, the total cumulative amounts of fentanyl base administered to the patient was 100, 300, 600, 1,000 and 1,400 μ g of fentanyl base. The plasma levels of fentanyl base found in the patient were determined in nanograms of fentanyl per milliliter of plasma.

The results shown in Figure 1 indicate that the fentanyl appears in the patients blood within seconds after the administration by the interpulmonary route in accordance with the methodology and using the formulation of the present invention. The results are surprising in

- 33 -

that particularly large percentage amounts of fentanyl are delivered to the patient based on the amount of fentanyl actually administered to the patient by the interpulmonary route. Further, the results are
5 surprising in view of the relatively short time period from administration to the time period when the fentanyl actually appears in the patients blood.

In a previously published study of 30 patients treated for post-operative pain with intravenous fentanyl
10 patient-controlled analgesia, the minimum effective concentration (MEC) of fentanyl in the blood required to achieve pain relief in the group of patients studied was found to range from 0.23 to 1.18 ng/ml. (See Gourlay et al. cited above). Accordingly, the formulation and
15 methodology of the present invention can be used to quickly and efficiently achieve pain relief.

By using the formulations and methodology of the present invention it is possible to obtain a blood level of narcotic in the patient which is sufficient to
20 provide for pain relief in a period of time of five seconds or less. Specifically, it is possible to obtain a blood level of narcotic such as fentanyl in the patient by administering a dose of formulation containing 100 μ g of fentanyl base and thereby obtain a blood level above
25 1.5 ng/ml which is above the amount shown to provide for pain relief. Additional doses can be administered in order to provide for a higher degree of pain relief. This is clearly shown within figure 1. For example, by administering 300 μ g of fentanyl base it is possible to
30 obtain a blood level above 4.0 ng/ml. By administering 1,400 μ g of fentanyl base it is possible to obtain a blood level above 6.0 ng/ml which amount is sufficient to provide for pain relief from even severe pain. Thus, the invention can be used to administer 50 μ g to about
35 2,000 μ g of narcotic to a patient by inhalation and

-34-

obtain a blood level in the range of 1.5 to 6.5 ng/ml in
a period of time of less than 1 minute. Thus the
formulations and methodology of the invention provide for
a means to obtain high levels of a narcotic in the blood
5 plasma of a patient in a very short period of time.

The instant invention is shown and described
herein in what is considered to be the most practical and
preferred embodiments. It is recognized, however, that
10 the departures may be made therefrom which are within the
scope of the invention and that obvious modifications
will occur to one skilled in the art upon reading this
disclosure.

15

20

25

30

35

-35-

CLAIMS

1. An aerosol formulation in the form of a solution, consisting essentially only of:

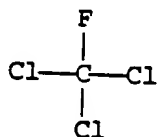
5 a narcotic selected from the group consisting of a free base form of drug selected from the group consisting of fentanyl, sufentanil, and remifentanyl; and

10 a propellant with the narcotic being completely dissolved in the propellant.

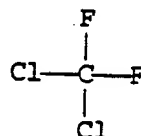
2. The formulation of claim 1, wherein the narcotic is present in an amount in the range of from about 0.01% to about 1% by weight based on the total
15 volume of the formulation.

3. The formulation of claim 1, wherein the narcotic is completely dissolved in the propellant.

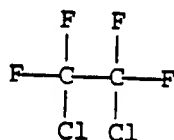
20 4. The formulation of claim 1, wherein the propellant has a structure selected from the group consisting of:



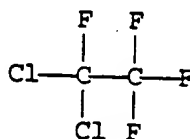
Formula I



Formula II

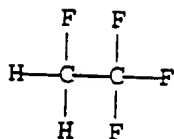


Formula III

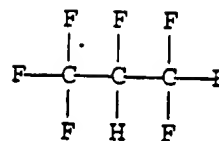


Formula IV

-36-



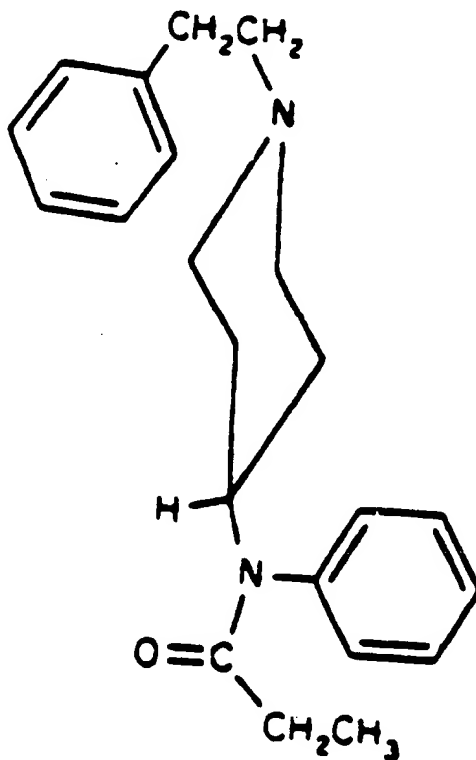
Formula V



Formula VI

wherein C is carbon, H is hydrogen, F is fluorine and Cl is chlorine.

5. The formulation of claim 1, wherein the narcotic has the following general structural formula:

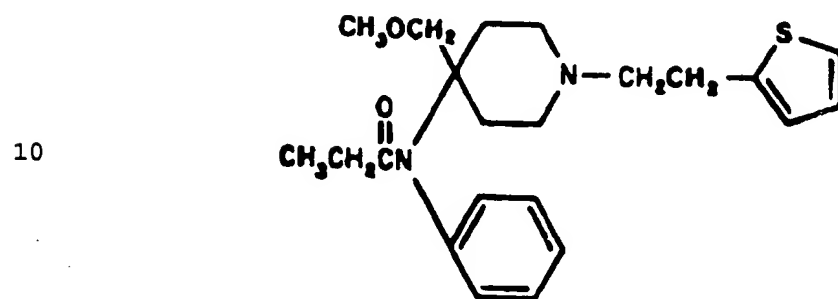


wherein C is carbon, N is nitrogen, H is hydrogen and O is oxygen.

- 37 -

6. The formulation of claim 1, wherein the narcotic has the following general structural formula:

5



10

15

wherein C is carbon, N is nitrogen, H is hydrogen, O is oxygen and S is sulfur.

20

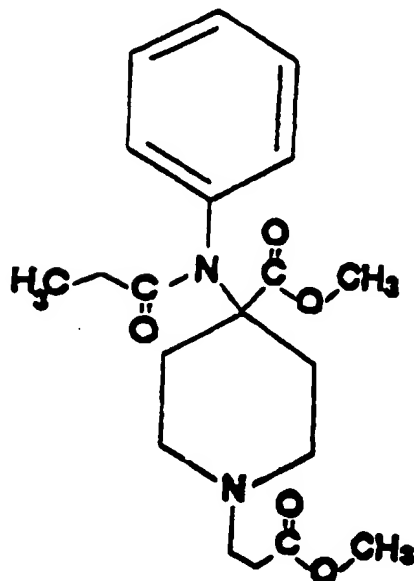
25

30

35

-38-

7. The formulation of claim 1, wherein the narcotic has the following general structural formula:



wherein C is carbon, N is nitrogen, H is hydrogen and O is oxygen.

8. An aerosol formulation in the form of a solution, consisting essentially only of:

a narcotic selected from the group consisting of a free base form of drug selected from the group consisting of fentanyl, sufentanil, and remifentanyl;

a lubricant; and

a propellant with the narcotic being completely dissolved in the propellant;

wherein the propellant and lubricant are both non-polar or both polar and wherein the lubricant does

-39-

not significantly effect the solubility of the narcotic in the propellant.

9. The formulation of claim 8, wherein the
5 propellant and lubricant are both polar.

10. The formulation of claim 8, wherein the propellant and lubricant are both non-polar.

10 11. The formulation of claim 8, wherein the propellant is a hydrofluoroalkane and the lubricant is a polyethylene glycol.

15 12. The formulation of claim 8, wherein the propellant is a chlorofluorocarbon and the lubricant is a saturated vegetable oil.

13. A method of intrapulmonary administration of a narcotic drug, comprising:
20 releasing a metered dose of formulation from a pressurized canister wherein the formulation is comprised of a narcotic selected from the group consisting of fentanyl, sufentanil, and remifentanyl in an amount of 50 μ g or more in combination with a propellant;
25 inhaling the metered dose of formulation into the lungs of a patient and obtaining a blood plasma level of narcotic of above 1.5 ng/ml within 30 seconds or less from the inhaling.

30 14. The method of claim 13, wherein the drug is fentanyl.

15 15. The method of claim 13, wherein the drug is remifentanyl.

35

-40-

16. The method as claimed in claim 13, wherein the drug is sufentanil.

17. The method as claimed in claim 13, wherein
5 the drug is administered in an amount in the range of
from about 50 μg to about 2,000 μg .

18. The method claim 17, wherein the plasma
blood level obtained is in the range of 1.5 to 6.5 ng/ml
10 in a period of time of less than one minute.

15

20

25

30

35

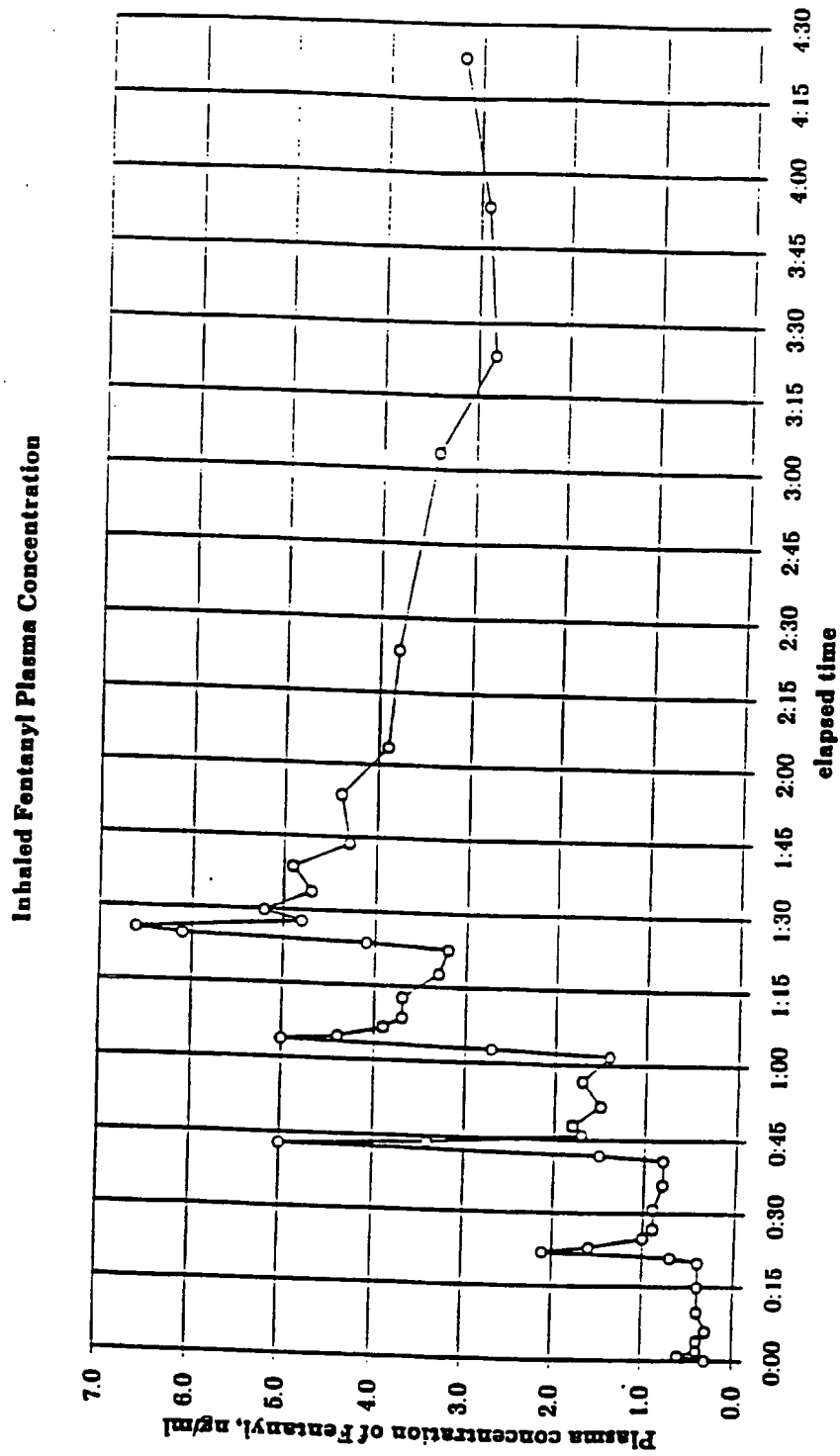


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/05798

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/12

US CL : 424/45

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/45

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A, 90/07333 (RIKER LABORATORIES, INC.) 12 July 1990, see entire document.	1-18
Y	Pharmacology Biochemistry and Behavior, Volume 44, No 1, d 1993, (WEINHOLD ET AL), "Housing Conditions Influence Acquisition of Sufentanil Aerosol Self-Administration in Rats", pages 141-144.	1-18

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

A documents defining the general state of the art which is not considered to be part of particular relevance

E earlier documents published on or after the international filing date

L documents which may throw doubts on priority claims) or which is cited to establish the publication date of another citation or other special reason (as specified)

O documents referring to an oral disclosure, use, exhibition or other means

P documents published prior to the international filing date but later than the priority date claimed

T

later documents published after the international filing date or priority date and not in conflict with the application but cited to understate the principle or theory underlying the invention

X

document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z

document member of the same patent family

Date of the actual completion of the international search

22 JUNE 1995

Date of mailing of the international search report

08 AUG 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Raj Bawa, Ph.D.

Telephone No. (703) 308-2351